Tetrahedron Letters No.24, pp. 2661-2668, 1966. Pergamon Press Ltd.
Printed in Great Britain.

HIGH RESOLUTION NMR INVESTIGATION OF ENOLIZATION OF ETHYL α-ALKYLACETOACETATES AND 3-ALKYLACETYLACETONES WITH BRANCHED SUBSTITUENTS.

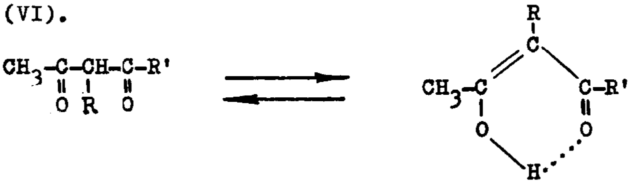
S.T.Yoffe, E.I.Fedin, P.V.Petrovskii
and M.I.Kabachnik

Institute of Organo-Element Compounds
Academy of Sciences of USSR

(Received 9 April 1966)

Keto-enol equilibrium of ethyl α-alkylacetoacetates and 3-alkylacetylacetones in different solvents has been recently studied by M.I.Kabachnik, S.T.Yoffe, K.V.Vatsuro and E.M.Popov using bromometrical method and UV- and IR-spectra (1,2,3). Later in these compounds the application of GLC showed the presence of some O-alkyl-derivatives (4,5) accepted by us as trans-enolic form. So, not having direct proves of trans-enolization of such compounds, we used NMR Spectra for solving of this problem. Yu.N.Molin, S.T.Yoffe, E.E.Saev, E.K.Solov'eva, E.E.Kugutcheva, V.V.Voevodskii and M.I.Kabachnik investigated the keto-enol equilibrium of 3-alkylacetylacetones using the NMR Spectra (6). No presence of enolic form was detected in 3-isopropylacetylacetone (I) and 3-sec.butylacetylacetone (II), where the branched substituents form steric hindrances for cis-enolization. Later other authors have found about 1% of enol (7) for ethyl α-isopropylacetoacetate (III) (NMR) and 0,75–1% (4) and 0,4% of enol (8) for ethyl α-sec.butylacetoacetate (IV) (bromometrical titration).

In this work high resolution NMR Spectra were investigated for compounds I-IV, ethyl α-(3-pentyl)-acetoacetate (V) and ethyl α-(2-heptyl)acetoacetate (VI).



keton cis-enol

I. $R=i\text{-}C_3H_7$, $R'=CH_3$ II. $R=s\text{-}C_4H_9$, $R'=CH_3$

III. $R=i\text{-}C_3H_7$, $R'=OC_2H_5$ IV. $R=s\text{-}C_4H_9$, $R'=OC_2H_5$

V. $R=(C_2H_5)_2CH$, $R'=OC_2H_5$ VI. $R=n\text{-}C_5H_{11}(CH_3)CH$, $R'=OC_2H_5$

It was interesting to investigate the possibility of trans-enolization of substances with branched substituents using compounds with higher enolization. It is known that the replacing of CH_3- for CF_3- in ethyl acetoacetate leads to a higher enolization. So, ethyl acetoacetate contains 7,8% of enol and ethyl trifluoracetoacetate - 89% (7) (NMR). It might be supposed that higher enolization would be observed also in ethyl α -alkyltrifluoracetoacetates. Ethyl α -n-propyltrifluoracetoacetate (VII) and ethyl α -isopropyltrifluoracetoacetate (VIII) were synthesized and their NMR Spectra investigated.

Compounds I - VI prepared by the usual method (2,3) were additionally purified from O-alkylderivatives (4, 5) . Compound V was not purified. Substance VII was prepared by Claisen condensation of ethyl trifluoracetate with ethyl valerate in the presence of dry sodium ethoxide in ether (6 days boiling). The yield was 7.5% , b.p. 75-76° at 22 mm, n_D^{20} 1.3820, d_4^{20} 1.1361. $C_9H_{13}F_3O_3$. Calc.% C 47.8, H 5.8, F 25.2. Found % C 47.9, 48.2; H 5.9, 5.8; F 25.3, 25.0. Substance VIII was prepared by condensation of ethyl trifluoracetate with ethyl isovalerate in the presence of sodium hydride in dipropyl ether (15 hours at 50°) with the following purification by means of GLPC. The yield was 3.1%, b.p. 73° at 25 mm, n_D^{20} 1.3792, d_4^{20} 1.1333. $C_9H_{13}F_3O_3$. Calc.% C 47.8; H 5,8; F 25.2. Found % c 48.0, 48.2; H 5.9, 5.7; F 25.1, 25.0. NMR Spectra were obtained at 60 Mc/s at 34°C using a Hitachi-H-60 high resolution spectrometer. Chemical shifts are in p.p.m. relative to tetramethylsilane. The internal standart was hexamethyldisiloxane. The spin-spin splitting Constants (J) are in c.p.s. NMR Spectra of substances II, IV, VII are given on Fig.1.

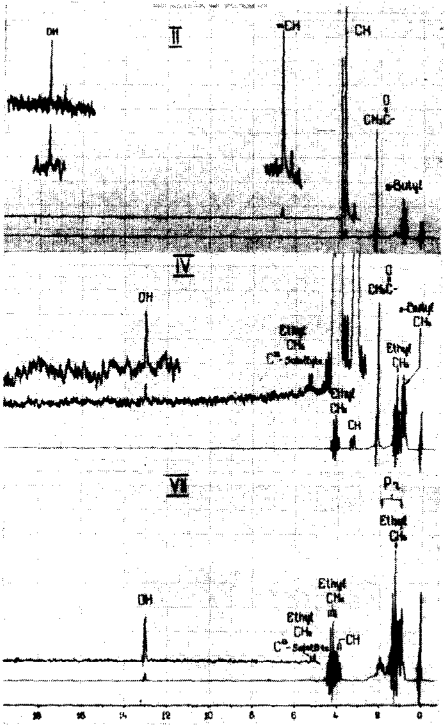


Fig.1

The NMR Spectra of substances II,IV and VII.

A sharp line in the region of 12.9 p.p.m. $\leqslant \delta \leqslant$ 17.5 p.p.m. (see table 1), corresponding to proton of OH cis-enolic form, was clearly seen above noises in substances I-VI and VIII. The large shift of this line proves, that the proton of hydroxyl is involved in intramolecular hydrogen bond forming a six-membered pseudoaromatic ring. As it might be expected substance VII was notably enolized. Here the OH-line is split into a quadruplet with intensity relation 1:3:3:1, due to interaction of the proton with three equivalent nuclei in CF_3 ($J = 2$ c.p.s.). In substances I,II and V the presence of O-derivatives was found, characterised by single signals of vinyl proton =CH (6.15, 6.60, 5.00 respectively). It is interesting to note that two doublets are seen ($J=11$c.p.s.) instead of one CH-doublet of ketonic form ($\delta = 3.4$ p.p.m.). This is possibly connected with the appearance of conformers due to asymmetry of molecules and volume of the replacing group. Such splitting does not take place in the case of α -isopropyl-substituent and for 3-alkylacetylacetones with more symmetrical molecules. The data received allow to evaluate the degree and character of enolization and the degree of O-isomerization and to compare these data with the GLC and bromometrical titration results. For the latter case the sum of cis-enol and O-ether is computed. The results are given in Table 1.

TABLE 1

Content of cis-enol and O-ether in ethyl α-alkylacetoacetates, 3-alkylacetylacetones and ethyl α-alkyltrifluoracetoacetates with branched substituents in percents.

Substituent in $CH_3COCHRCOOC_2H_5$	Cis-enol NMR	O-ether NMR	O-ether GLC	Bromometry cis-enol+O-ether
i-C_3H_7	0.1(12.9)*)	0	0	0.4
s-C_4H_9	0.4(13.1)	0	0	0.4
$(C_2H_5)_2CH$	1.4(13.3)	1.5	-	-
n-$C_5H_{11}(CH_3)CH$	0.2(12.9)	0	-	-
Substituent in $CH_3COCHRCOCH_3$				
i-C_3H_7	0.1(17.3)	0.3	0	0.6
s-C_4H_9	0.7(17.5)	2.3	1.9	2.4
Substituent in $CF_3COCHRCOOC_2H_5$				
n-C_3H_7	18(13.05)	0	0	-**)
i-C_3H_7	0.3(13.1)	0	0	-

*) The chemical shift δ (OH) in p.p.m. is shown in brackets.

**) As it known (9)bromometrical titration of substances, containing CF_3 - does not give satisfactory results.

These results show that contrary to the original assumption about trans-enolization based on studying of keto-enol equilibrium in different solutions without NMR (1,2,3), substances I-VIII contain only the cis-enolic form. Steric hindrances of cis-enolization in the presence of branched substituents do not lead to the formation of trans-enolic forms, but to a greater content of energeticaly more stable ketonic forms. This is clearly seen from comparison of the enolization substances VII and VIII. The presence of a n-propyl-substituent in compound VII still keeps rather a high level of enolization (18%), though it diminishes the enolization in comparison with ethyl trifluoracetoacetate. The introduction of a branched substituent increases steric hindrances and diminishes the content of enol to 0,3%. Differences in enolization of compound III (which is $\leqslant$ 0,1% according to our data; the data of other authors (7) about 1%) seem to be connected with different degrees of purity of investigated substances. Though there are no trans--enolic forms in compounds I-VIII, still there exist and were isolated cis-(IX) and trans-O-methylacetylacetones (X) (10).

The differences in b.p. and m.p. and conversion of the less stable cis-IX into trans-X when heated are proves for geometrical isomerism of these substances. According our data cis-IX and trans-X differ greatly in n_D: cis-IX n_D^{20} 1.4915; trans-X n_D^{20} 1.4670. The UV-Spectra are almost identical. We have investigated the NMR Spectra cis-IX and trans-X and found a notable difference in chemical shifts of vinylic proton=CH in both isomers. For IX δ(=CH)=4.97, for X δ(=CH)=5.55. These data allow to determine the stereochemical configuration of O-ethyl-acetylacetone (XI) prepared by alkylating of Ag-salt of acetylacetone with ethyl-iodide(11). Substance XI shows a chemical shift δ (=CH)=5.51 and is therefore, a trans-ether.

REFERENCES

1. M.I.Kabachnik, S.T.Yoffe,K.V.Vatsuro,*Tetrahedron* **1**,317(1957).
2. M.I.Kabachnik, S.T.Yoffe, E.M.Popov and K.V.Vatsuro *Tetrahedron* **12**, 76 (1961).
3. S.T.Yoffe, E.M.Popov, K.V.Vatsuro, E.K.Tulikova and M.I.Kabachnik *Tetrahedron* **18**, 923 (1962).
4. S.J.Rhoads, R.W.Hasbrouck, C.Pryde,R.W.Holder *Tetrahedron Letters* **1963** ,669.
5. S.T.Yoffe, K.V.Vatsuro, E.E.Kugutcheva and M.I.Kabachnik *Tetrahedron Letters* **1965**, 593.
6. Yu.N.Molin, S.T.Yoffe, E.E.Saev, E.K.Solov'eva, E.E.Kugutcheva, V.V.Voevodskii and M.I.Kabachnik, *Izvest.Akad.Nauk SSSR.Ser.chim.*,**1965**, 1556.
7. J.L.Burdett, M.T.Rogers.*J.Amer.Chem.Soc.* **86**, 2105 (1964).
8. S.J.Rhoads, C.Pryde *J.Org.Chem.* **30**, 3212 (1965).
9. R.Filler, S.M.Naqvi *J.Org.Chem.* **26**, 2571 (1961).
10. B.Eistert, F.Arndt, L.Loewe, E.Ayca *Ber.* **84**, 156 (1951).
11. R.S.Curtiss, *Am.Chem.J.* **17**,435 (1895).